REMARKS

New claims 33-59 have been added to more particularly point out and distinctly claim various aspects of the invention. A clean copy of all pending claims, including the new claims is included. No new matter has been added. The specification has been amended to address the sequence listing requirements, and a substitute sequence listing, both paper and computer readable, has been submitted.

Claim rejections

Claims 1, 2, 4, 10-12 and 32 are rejected under 35 U.S.C. §102(b) as being anticipated by Tollefson et al. (J. Virol. 70:2296-2306). Bett is cited as evidence of the structure of *dl*309.

Claim 1 calls for a recombinant adenovirus vector which, among other things, overexpresses an adenovirus death protein (ADP). The Office alleges that Tollefson et al. disclose an adenovirus, *dl*309, and that *dl* 309 is capable of overexpressing an adenovirus death protein. Tollefson et al. do not disclose or suggest that dl309 is capable of overexpressing ADP. Rather, the Office relies on a statement from the instant specification to support the conclusion that *dl*309 overexpresses ADP. Specifically, the instant application states that "[g]enerally, any type of deletion in the E3 region that removes a splice site for any of the E3 pre-mRNAs will lead to overexpression of the mRNA for ADP...." Since *dl*309 comprises a deletion that removes a splice site for the 14.7K protein, the Office concludes that *dl*309 overexpresses ADP.

The statement in Applicant's specification that the Office refers to is believed by the inventors to be generally true, and sufficiently accurate to support a reasonable expectation that overexpression of ADP may be achieved on that basis. In fact, several working embodiments provided in the Examples support that statement. KD1, KD2, KD3, GZ1 and GZ3 all comprise deletions of portions of the E3 region that comprise splice sites for E3 proteins other than ADP, and all have been shown to overexpress ADP (See Examples).

Although the statement relied on by the Office is in fact generally true, Applicant respectfully points out that the Examiner has provided no evidence that *dl*309 overexpresses ADP. In fact, the available evidence suggests to the contrary; that dl309 expresses normal, wild-type levels of ADP. Figure 2 of Tollefson et al. shows a plaque assay in which Ad5, a wild type adenovirus is assayed side-by-side with *dl*309, among other adenoviruses. Note that the plaque size and morphologies are extremely similar as between Ad5 and *dl*309. Plaque size and morphology are indicators of cell lysis, which is strongly correlated to ADP expression. Thus, the skilled artisan would conclude from Tollefson et al. that ADP expression is the same as between Ad5 (wild type) and *dl*309. Further, Figure 3 illustrates the rate of plaque development for the experiment whose results are shown in Figure 2. Note that Ad5 (wild type) and *dl*309 have almost identical plaque development rates. This again supports the conclusion that *dl*309 has wild type expression of ADP.

In addition, the instant specification teaches that *dl*309 has wild-type expression of ADP. (See Figures 2 and 5 and the discussion at page 24, lines 11-23 and 28-32). Figure 2 shows an immunoblot of proteins isolated from A549 cells infected with various viruses, including *dl*309 and KD1, KD3, GZ1 and GZ3. Note that *dl*309 shows no ADP expression at 24 hours p.i., and very little ADP expression at 36 hours p.i., relative to the overexpression shown by the KD and GZ vectors. Figure 5 is a cell spread assay that shows that *dl*309 spreads from cell to cell at a similar rate as the wild-type Ad5. Here, the crystal violet stains live cells, but not dead ones. Since cell lysis (death) is correlated with ADP expression, the assay indirectly measures ADP expression. Note that KD1 and KD3 cause lysis (death) more quickly than both Ad5 and *dl*309. Thus, the skilled artisan would conclude based on this evidence, that *dl*309 does not overexpress ADP.

The Office has failed to present any credible evidence that Tollefson et al. teaches overexpression of ADP. In re Spada, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("the reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it"). Here, the evidence in both Tollefson et al. and in the instant

specification leads a person of ordinary skill to conclude that *dl*309 does not overexpress ADP. Tollefson et al. does not address the issue of overexpression of ADP. Since Tollefson et al. fails to teach an Ad vector that overexpresses ADP, and since the instant claims are limited to those Ad vectors that overexpress ADP, Tollefson et al. cannot anticipate the instant claims.

Claims 1, 2, 4 and 10-13 are rejected under 35 U.S.C. §102(e) as being anticipated by Henderson et al. and separately by Little et al. In addition, claims 13, and 20-22 are rejected under 35 U.S.C. §103(a) as being obvious either over Little in view of Freytag et al. or separately over Henderson in view of Freytag et al. Since all of these rejections rely on the Little and Henderson references, the arguments below that address those references will overcome the rejections that rely on them either exclusively under §102(e) or as the primary reference under §103(a).

All of the rejected claims call for a recombinant adenovirus vector which, among other things, overexpresses an adenovirus death protein (ADP). Henderson et al. is cited by the Office as teaching "an E3-deleted replication-competent adenovirus, CN751, capable of overexpressing an adenovirus death protein...." (Office Action of 3/15/01) The Office does not elaborate on this conclusory statement, nor point to any particular evidence that suggests that CN751 overexpresses ADP.

Applicant respectfully points out that the Office has provided no evidence that CN751 overexpresses ADP. In fact, the available evidence suggest to the contrary, that CN751 expresses normal, wild-type levels of ADP. Examples 4 and 6 demonstrate that CN751 expresses wild-type levels of ADP. The experiments described in those examples include three viruses: CN751, CN702 and *rec*700. CN751 has an E3 deletion, and has the ADP orf inserted into the E3 deletion. CN702 is identical to wild-type Ad5, except that it has a large deletion in the E3 region that removes most of the E3 genes including the ADP gene. *Rec*700 is an Ad5-Ad2-Ad5 recombinant that consists of the Ad5 EcoR-A fragment (map position 0-76), the Ad2 EcoR-D fragment (map position 76-83) and the Ad5 EcoRI-B fragment (map position 83-100). *rec*700 has the Ad2 ADP. Several published reports demonstrate that *rec*700 synthesizes normal,

wild-type levels of ADP (Tollefson, A.E. et al., *Journal of Virology* 66:3633-3642, (1992); Scaria, A. et al., *Virology* 191:743-753, (1992)). Skilled artisans have routinely used *rec*700 as the wild-type control in studies that analyze the phenotype of mutants that lack a functional gene for ADP (Tollefson et al., *Journal of Virology* 70:2296-2306, (1996); Tollefson et al., *Virology* 220:152-162, (1996)). In the experiment described in example 6 of Henderson et al., the ability of CN751, CN702 and *rec*700 to lyse cultured LNCaP cells is compared (see Figure 10). As discussed above, cell death is correlated with ADP expression. The results indicate that CN751 kills cells similarly to *rec*700, both of which kill cells more efficiently than CN702. As Henderson et al. state: "[t]he results suggest that CN751 kills cells more efficiently than the adp- control, CN702, and similarly to the adp+ control, *rec*700." (column 49, lines 6-8 of Henderson et al.). Therefore, since *rec*700 expresses wild-type, i.e. "normal", levels of ADP, it follows that CN751 also expresses wild-type levels of ADP. Thus, the evidence suggests that CN751 does not overexpress ADP. Applicant further points out that there is no discussion or suggestion in Henderson et al. of overexpression of ADP, either by the CN751 vector, or in general. Thus, Henderson et al. does not teach an E3-deleted replication-competent adenovirus capable of overexpressing an adenovirus death protein, as alleged by the Office, and therefore cannot anticipate the instant claims. Nor can Henderson support the rejections under 103(a) that rely on that teaching.

Little et al. is cited as teaching "...a recombinant vector which is replication competent and which overexpresses ADP." (Office Action of 8/24/01). Specifically, the Office alleges that CN751 overexpresses ADP. (O/A of 8/24/01 at page 19). The Office relies on the data presented at column 40, lines 34-53, which indicates that CN751 kills cells more efficiently and releases 10-40 times more virus at 48-72 hours post-infection as compared to a replication competent adenovirus lacking adp.

Applicant respectfully points out that, as discussed above, the Office has provided no evidence that CN751 overexpresses ADP, as required by the instant claims. The data relied on by the Office does not address the issue of overexpression of ADP, because there is no wild-type control virus in the studies presented in Little et

al. Those studies compared CN751 to a virus that lacks the gene that encodes ADP. Therefore, the fact that CN751 kills more efficiently, and releases more virus than the adp- virus only suggests that CN751 *expresses* ADP, and is insufficient to lead a skilled artisan to conclude that CN751 *overexpresses* ADP. In fact, as discussed above, when compared to a virus that expresses wild-type levels of ADP, CN751 kills with similar efficiency and releases similar levels of virus, and thus the skilled artisan would conclude that the evidence suggests that *CN751 expresses wild-type levels of ADP.* Thus, Little et al. does not teach a recombinant vector which is replication competent and which overexpresses ADP, as alleged by the Office, and therefore cannot anticipate the instant claims. Nor can Little et al. support the rejections under 103(a) that rely on that teaching.

Further, both of the patents (Henderson et al. and Little et al.) relied on in support of the 102(e) and 103(a) rejections are effective as prior art, at the earliest, as of March 3, 1997. Since all of those rejections rely on the Little and Henderson references, antedating those references will overcome the rejections that rely on them either exclusively under §102(e) or as the primary reference under §103(a).

Included herewith is a Declaration under 37 C.F.R. §1.131 signed by each of the inventors that establishes that the inventors of the embodiments of the claims at issue and rejected in the Office Action dated July 5, 2002 conceived of the claimed invention prior to March 3, 1997, and further establishes that the inventors worked diligently towards reducing the invention to practice continuously and uninterrupted from at least prior to March 3, 1997 until actual reduction to practice was achieved. Specifically, the declaration establishes that KD1 was conceived of prior to March 3, 1997, and that the inventors worked diligently, continuously and uninterrupted until KD1 was reduced to practice.

Claim 1 of the instant application is directed to a recombinant adenovirus vector that is replication competent in neoplastic cells and that overexpresses ADP. As stated in the declaration, "KD1 is a recombinant adenovirus vector that is replication competent

in neoplastic cells and that overexpresses ADP." "Replication competent" is defined in the specification as follows:

> "Replication-competent" as applied to a vector means that the vector is capable of replicating in normal and/or neoplastic cells. As applied to a recombinant virus, "replication-competent" means that the virus exhibits the following phenotypic characteristics in normal and/or neoplastic cells: cell infection; replication of the viral genome; and production and release of new virus particles; although one or more of these characteristics need not occur at the same rate as they occur in the same cell type infected by a wild-type virus, and may occur at a faster or slower rate.

KD1 is capable of replicating in neoplastic cells. KD1 overexpresses ADP. Thus, KD1 reads on claim 1. The declaration (supported by the documentary evidence cited therein and included herewith as Exhibits A-L) establishes that KD1 was made prior to March 3, 1997, and that diligence continued uninterrupted until at least May 20, 1997, when it was demonstrated that KD1 overexpresses ADP. In view of the evidence presented in the declaration, establishing that the claimed invention was conceived of prior to March 3, 1997 and that diligence continued uninterrupted at least until KD1 was reduced to practice, Applicant respectfully requests that the rejections under 35 U.S.C. §§102 and 103 be withdrawn.

Claims 1, 2, 4 and 10-13 are rejected under the doctrine of obviousness-type double patenting over claims 1-10 of copending Application No. 09/956,335. Since the claims of that application have not yet issued, Applicant defers addressing this rejection until such time as those claims are patented.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office

Action, and as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, he is invited to telephone the undersigned at the number provided.

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1. A recombinant adenovirus vector which is replication-competent in neoplastic cells and which overexpresses an adenovirus death protein.

2. The adenovirus vector of claim 1 wherein the adenovirus death protein comprises SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, [or] SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.

4. The recombinant adenovirus vector of claim 2, wherein the recombinant adenovirus lacks expression of at least one E3 protein selected from the group consisting of: gp19K; RIDα; RIDβ and 14.7K.

5. The recombinant adenovirus vector of claim 4, wherein the recombinant adenovirus comprises SEQ ID NO:1 or SEQ ID NO:2.

10. A method for promoting death of a neoplastic cell comprising contacting the neoplastic cell with an adenovirus vector, wherein

(a) at least one adenoviral vector is introduced into the neoplastic cell, and

(b) said adenovirus vector is replication-competent in neoplastic cells and overexpresses an adenovirus death protein.

11. The method of claim 10 wherein the adenovirus death protein comprises SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, [or] SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11 or SEQ ID NO:12.

12. The method of claim 11, wherein the adenovirus vector comprises a recombinant adenovirus lacking expression of at least one E3 protein selected from the group consisting of: gp19K; RIDα; RIDβ and 14.7K.

13. The method of claim 12, wherein the neoplastic cell is contained in a tumor in a patient and the contacting step comprises administering the adenovirus vector to neoplastic cells of the tumor.

14. The method of claim 13, further comprising the step of passively immunizing the patient against the recombinant adenovirus.

15. The method of claim 14, wherein the recombinant adenovirus comprises SEQ ID NO:1 or SEQ ID NO:2.

20. The method of claim 13, further comprising treating the tumor with radiation.

21. The method of claim 20 comprising administering more than one distinct type of recombinant adenovirus to the tumor and treating the tumor with radiation, wherein at least one recombinant adenovirus is replication-defective.

22. The method of claim 13, further comprising treating the tumor with chemotherapy.

24. The method of claim 13, further comprising administering to the tumor one or more replication-defective adenoviruses, wherein each replication-defective adenovirus expresses an anti-cancer gene product, and wherein the recombinant adenovirus facilitates the spread of the replication-defective adenovirus in the tumor.

28. A recombinant adenovirus vector, wherein said adenovirus vector (a) is replication-restricted to dividing cells, (b) contains a mutation in the E1A gene, and (c) overexpresses an adenovirus death protein.

29. The recombinant adenovirus vector of claim 1 wherein the adenovirus vector comprises a mutation in an E1A gene that renders the adenovirus incapable of expressing an E1A viral protein which binds the pRB and the p300/CBP proteins.

30. The recombinant adenovirus of claim 1 wherein an E4 promoter of said recombinant adenovirus vector is substituted with a promoter, which is activated only in neoplastic cells.

31. The recombinant adenovirus of claim 30 wherein the promoter, which is activated only in neoplastic cells, is the surfactant protein B ("SPB") promoter.

32. The recombinant adenovirus of claim 1 which comprises a polynucleotide that encodes an E3-12.5K protein.

33. The recombinant adenovirus vector of claim 1, wherein the recombinant adenovirus lacks expression of at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ and 14.7K.

34. The recombinant adenovirus vector of claim 33, wherein the recombinant adenovirus lacks expression of the gp19K protein.

35, The recombinant adenovirus vector of claim 33, wherein the recombinant adenovirus lacks expression of the RIDα protein.

36. The recombinant adenovirus vector of claim 33, wherein the recombinant adenovirus lacks expression of the RIDβ protein.

37. The recombinant adenovirus vector of claim 33, wherein the recombinant adenovirus lacks expression of the 14.7K protein.

38. The recombinant adenovirus vector of claim 33, wherein the recombinant adenovirus lacks expression of the gp19K, RIDα, RIDβ and 14.7K proteins.

39. The recombinant adenovirus vector of claim 1, wherein the recombinant adenovirus comprises a deletion in the E3 region that removes a splice site for any of the E3 mRNAs.

40. The recombinant adenovirus vector of claim 1, wherein the recombinant adenovirus comprises at least one deletion in the E3 region, wherein the at least one deletion comprises a sequence that encodes at least one E3 protein, wherein the protein is selected from the group consisting of gp19K, RIDα, RIDβ, 14.7K, 6.7K and 12.5K.

41. The recombinant adenovirus vector of claim 40, wherein the at least one deletion comprises a sequence that encodes the gp19K, RIDα, RIDβ and 14.7K proteins.

42. The recombinant adenovirus vector of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 6.7K protein.

43. The recombinant adenovirus vector of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 12.5K protein.

44. The recombinant adenovirus vector of claim 41, wherein the at least one deletion further comprises a sequence that encodes the 6.7K and 12.5K proteins.

45. A recombinant adenovirus vector, wherein said vector
(a) lacks expression of at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ and 14.7K; and
(b) comprises a gene that encodes ADP.

46. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the gp19K protein.

47. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the RIDα protein.

48. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the RIDβ protein.

49. The recombinant adenovirus vector of claim 45, wherein the E3 protein is the 14.7K protein.

50. The recombinant adenovirus vector of claim 45, wherein the vector lacks expression of the gp19K, RIDα, RIDβ and 14.7K proteins.

51. A recombinant adenovirus vector, wherein said vector comprises
(a) at least one deletion in the E3 region, wherein the at least one deletion comprises a sequence that encodes at least one E3 protein selected from the group consisting of gp19K, RIDα, RIDβ and 14.7K; and
(b) a gene that encodes ADP.

52. The recombinant adenovirus vector of claim 51, wherein the at least on deletion comprises a sequence that encodes the gp19K, RIDα, RIDβ, and 14.7K proteins.

53. The recombinant adenovirus vector of claim 51, wherein the at least one deletion further comprises a sequence that encodes the 6.7K protein.

54. The recombinant adenovirus vector of claim 51, wherein the at least one deletion further comprises a sequence that encodes the 12.5K protein.

55. The recombinant adenovirus vector of claim 51, wherein the at least one deletion further comprises a sequence that encodes the 6.7K and 12.5K proteins.

56. The recombinant adenovirus vector of claim 38, wherein the recombinant adenovirus lacks expression of the 6.7K protein.

57. The recombinant adenovirus vector of claim 38, wherein the recombinant adenovirus lacks expression of the 12.5K proteins.

58. The recombinant adenovirus vector of claim 38, wherein the recombinant adenovirus lacks expression of the 6.7K and 12.5K proteins.

59. The recombinant adenovirus of claim 51, wherein the at least one deletion comprises a splice site for any of the E3 mRNAs.